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Original Research Article

Comparison of deep inspiration breath hold and free breathing intensity modulated proton therapy of locally advanced lung cancer

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ABSTRACT

Background and purpose: For locally advanced non-small cell lung cancer (LA-NSCLC), intensity-modulated proton therapy (IMPT) can reduce organ at risk (OAR) doses compared to intensity-modulated radiotherapy (IMRT). Deep inspiration breath hold (DIBH) reduces OAR doses compared to free breathing (FB) in IMRT. In IMPT, differences in dose distributions and robustness between DIBH and FB are unclear. In this study, we compare DIBH to FB in IMPT, and IMPT to IMRT.

Materials and methods: Fortyone LA-NSCLC patients were prospectively included. 4D computed tomography images (4DCTs) and DIBH CTs were acquired for treatment planning and during weeks 1 and 3 of treatment. A new system for automated robust planning was developed and used to generate a FB and a DIBH IMPT plan for each patient. Plans were compared in terms of dose-volume parameters and normal tissue complication probabilities (NTCPs). Dose recalculations on repeat CTs were used to compare inter-fraction plan robustness.

Results: In IMPT, DIBH reduced median lungs D_{mean} from 9.3 Gy(RBE) to 8.0 Gy(RBE) compared to FB, and radiation pneumonitis NTCP from 10.9 % to 9.4 % ($p < 0.001$). Inter-fraction plan robustness for DIBH and FB was similar. Median NTCPs for radiation pneumonitis and mortality were around 9 percentage points lower with IMPT than IMRT ($p < 0.001$). These differences were much larger than between FB and DIBH within each modality.

Conclusion: DIBH IMPT resulted in reduced lung dose and radiation pneumonitis NTCP compared to FB IMPT. Inter-fraction robustness was comparable. OAR doses were far lower in IMPT than IMRT.

1. Introduction

Radiotherapy is standard of care for inoperable locally advanced non-small cell lung cancer (LA-NSCLC), combined with chemotherapy and followed by immunotherapy for certain subgroups [1,2]. Intensity-modulated photon radiotherapy (IMRT) with static beams or as volumetric arc therapy is the most common radiotherapy technique. LA-NSCLC patients often need extensive radiation fields, and radiation to the lungs, heart and esophagus causes frequent and potentially severe side effects [3].

Proton therapy has advantageous depth dose characteristics, and state-of-the-art intensity-modulated proton therapy (IMPT) allows conformal dose distributions that could reduce side effects in LA-NSCLC patients [4,5]. Compared to IMRT, IMPT dose distributions are more sensitive to inter-fraction variations in patient setup and changes in anatomy [6,7]. However, robust optimization algorithms can take the specific treatment uncertainties of IMPT into account during planning.

Radiotherapy of LA-NSCLC is usually performed in free breathing (FB), with a planning margin around the tumor to ensure dose coverage in all breathing phases. Deep inspiration breath hold (DIBH) is an alternative technique where patients hold their breath at a specific level of inspiration during radiotherapy delivery, potentially increasing the separation between the target volume and organs at risk (OARs) and allowing smaller margins due to elimination of breathing motion [8]. In photon radiotherapy of LA-NSCLC, DIBH reduces radiation dose to the lungs and heart and consequently normal tissue complication probabilities (NTCPs) for radiation pneumonitis and 2-year mortality compared to FB treatment [9–11], while plan robustness against inter-

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fraction changes is similar [9]. It is not clear whether DIBH has the same advantages in proton therapy of LA-NSCLC.

In this study we investigate DIBH in IMPT of LA-NSCLC and compare it to FB treatment, focusing on dose-volume parameters, NTCPs and inter-fraction robustness. Automated, scripted IMPT treatment planning was implemented to reduce planner bias. To put the results in perspective we also compare IMPT to IMRT plans.

2. Materials and method

2.1. Patients and images

Fortyone patients receiving radiotherapy with curative intent for LA-NSCLC at Haukeland University Hospital between October 2019 and November 2022 participated in prospective collection of FB and DIBH CT images. The study was approved by the regional committee for medical and health research ethics in Western Norway (protocol code 2019/749) and all participants gave informed consent. The prescribed dose was 60 or 66 Gy for concomitant treatment and 66 or 70 Gy for sequential treatment (depending on lung function, lung dose and proximity of the brachial plexus to the target), in 2 Gy fractions. Patient and treatment characteristics are summarized in Supplementary Materials S1.

The imaging, gating and delineation procedures have been described in detail in previous work [9]. Briefly, a 10-phase FB 4DCT and 3 DIBH CTs were acquired for planning, and a repeat FB 4DCT and DIBH CT were acquired during the first week (w1) and third week (w3) of treatment. For simulation of FB treatment, OARs and target volumes were delineated and planning was performed on the average intensity projection of the 4DCT. The gross tumor volume (GTV) positions in all 4DCT phases were incorporated in the internal GTV (IGTV). For simulation of DIBH treatment, OARs and target volumes were delineated and planning was performed on one DIBH CT, and the IGTV also incorporated the GTV positions in the two other DIBH CTs. In w1 and w3 only one DIBH repeat CT was acquired, hence no IGTV was delineated. The clinical target volume (CTV) margin was 5 mm both for FB and DIBH. A Big Bore CT scanner (Philips Healthcare, Best, The Netherlands) was used for imaging and DIBH was monitored with the Respiratory Gating for Scanners system (Varian Medical Systems, Palo Alto, USA).

2.2. Automated IMPT treatment planning

Automated, scripted IMPT treatment planning was implemented in RayStation v12 (RaySearch Laboratories, Stockholm, Sweden). All IMPT plans in this study were automatically generated by the planning script. The main steps performed by the script were: (1) add fixed objectives for CTV (uniform dose, robust) and patient body (max dose and dose fall-off around the CTV) and run optimization, (2) add personalized objectives for OARs based on achieved OAR doses in step 1, reset beams and run new optimization, (3) if achieved dose for lungs, heart and/or esophagus is lower than objective, lower objective further, reset and run new optimization (starting from 2), and (4) compute final dose.

A detailed overview of the planning script including optimization objectives and priorities is given in Supplementary Materials S2 and the script is available on GitHub (https://github.com/kristinefjellanger/LungIMPT.git). The autoplans were validated against manually created plans from a previous study for 5 patients, and similar or better plans were achieved for all patients [6].

Planning objectives are listed in Supplementary Materials S3. Proton doses are radiobiologically equivalent, i.e. physical dose multiplied by a constant relative biological effectiveness (RBE) factor of 1.1. Dose to the CTV was robustly optimized (minimax optimization [12] with 5 mm setup and 3.5 % range uncertainty) [6]. A density override representative for tumor tissue (1.06 g/cm^3) was used for the IGTV on the average intensity projections [13].

Prior to the automated planning, beam angles were manually selected for each patient, and the same field setup was used in the FB and DIBH plans. Most patients had 3 co-planar fields with 30°-40° separation, while 4–5 co-planar fields with field specific targets were used in some cases with separated target volumes. A 4 cm range shifter was used for shallow targets, and air gaps between the most downstream beam modifier and the patient contour were 5 cm. The dose grid was 3 mm and the plans were normalized to the median dose in the CTV. Machine settings for a Varian ProBeam system were used for planning and a Monte Carlo algorithm with 0.5 % statistical uncertainty was used for dose calculation.

2.3. Comparison of FB and DIBH

To assure that the plans were indeed robust at planning, robustness towards setup and range uncertainties, breathing motion (FB) and inter-breath-hold variability (DIBH) was evaluated (Supplementary Materials S4).

CTV and OAR dose-volume parameters were compared between nominal FB and DIBH plans. NTCPs for radiation pneumonitis grade ≥ 2, 2-year mortality and acute esophageal toxicity grade ≥ 2 were calculated to assess clinical relevance of dose differences in OARs [14–17]. The effective radiation dose to immune cells in circulating blood was calculated based on the model of Jin et al. [18]. The models are described in Supplementary Materials S5.

FB and DIBH CTs from w1 were available for 40 patients and from w3 for 37 patients. To compare inter-fraction robustness of FB and DIBH plans, the w1 and w3 CTs were rigidly registered to the corresponding planning CT using three degrees of freedom and focus on bone. OARs and target volumes were re-delineated on the repeat CTs. The FB and DIBH plans were recalculated on the corresponding w1 and w3 CTs, and any violations of the clinical goals for the CTV and patient body were recorded.

2.4. Comparison of IMPT and IMRT

The FB and DIBH IMPT plans generated in this study were compared to FB and DIBH IMRT plans from a previous simulation study, where 38 patients from the same cohort were included [9]. All patients in that study were also included in the current study, and the same FB and DIBH CTs were used for the simulations. The IMRT plans were generated with the in-house iCE system for autoplanning [9,19].

2.5. Statistical analyses

Statistical analyses were performed in SPSS Statistics v. 26 (IBM Corp., Armonk, USA). The two-tailed Wilcoxon signed-rank test was used for related samples. This study was evaluated using the RATING criteria for treatment planning studies with a score of 94 % [20].

3. Results

3.1. Comparison of FB and DIBH at planning

The average CTV volumes were 242 cm^3 (FB) and 224 cm^3 (DIBH), and average lung volumes were 3752 cm^3 (FB) and 5628 cm^3 (DIBH).

Evaluations of robustness on the planning scans confirmed that the planning strategy produced acceptably robust plans at baseline (Supplementary Materials S4). In the nominal scenario, DIBH reduced the mean lung dose for 90 % of patients compared to FB (Fig. 1a). The median lung D_{mean} was reduced from 9.3 to 8.0 Gy(RBE), and $V_{5Gy(RBE)}$ and $V_{20Gy(RBE)}$ were also substantially reduced (Table 1, Fig. 2a). This could be due to larger lung volumes and smaller CTV volumes with DIBH. The effective dose to immune cells was also lower with DIBH than FB (Table 1).

D_{2cc} in the patient body was higher with DIBH for 88 % of the patients, with a median of 103.8 % compared to 103.5 % with FB. This was

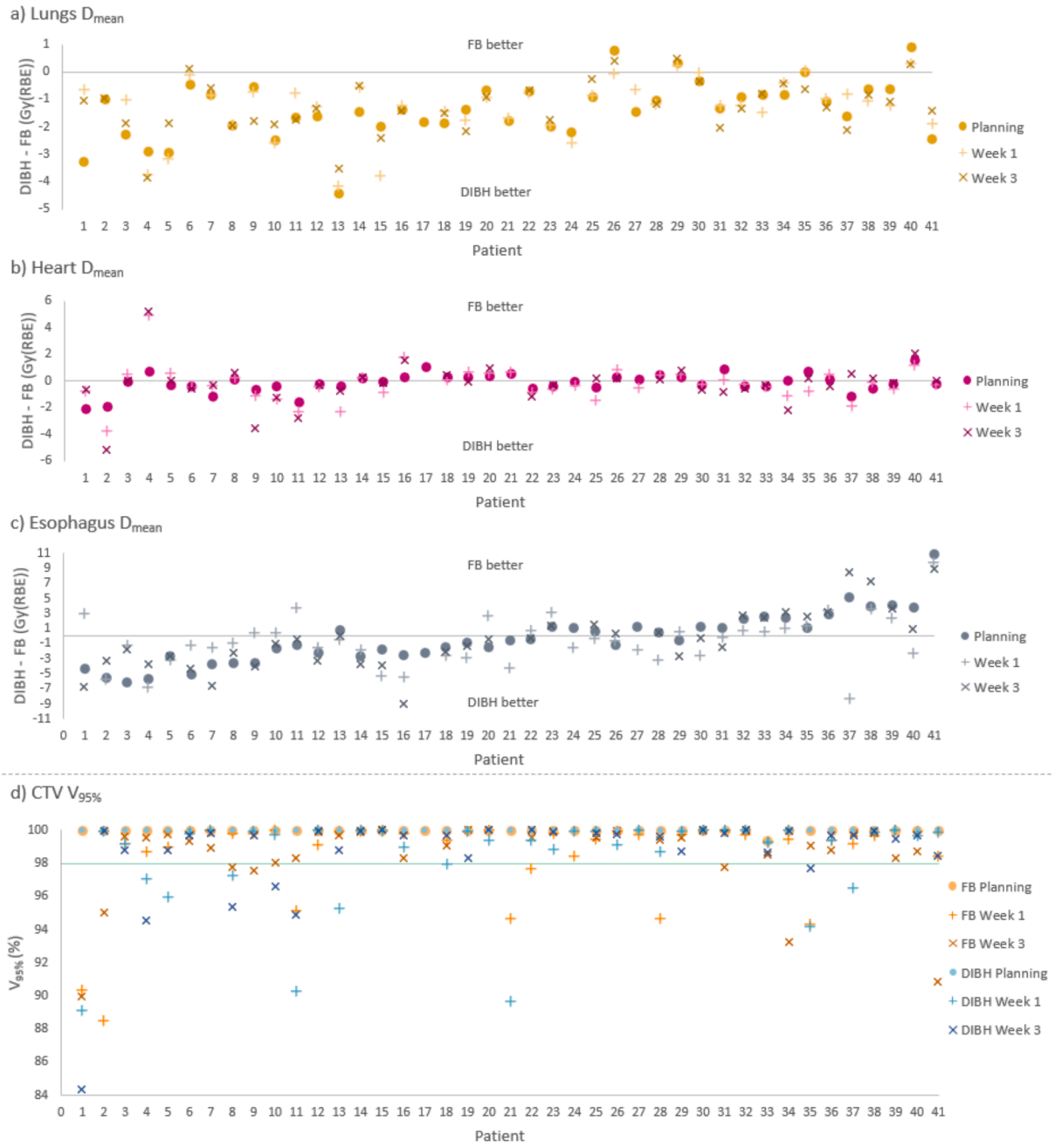

Fig. 1. a–c) Absolute differences between the DIBH and FB IMPT plans in D_{mean} for the lungs, heart and esophagus for each patient. d) CTV $V_{95\%}$ for each technique, with the green line indicating the objective of 98%. The values at planning, in w1 and w3 are represented by different symbols. For four patients missing one or both repeat CTs (patients 17, 21, 24 and 27), results are shown only for the other time points. The patients are sorted according to the sum of DIBH-FB differences for the three OARs. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

not considered an issue as no patients exceeded the clinical goal of D_{2cc} < 107 %. The CTV $V_{95\%}$, heart and esophagus D_{mean} and spinal canal D_{max} were similar for FB and DIBH (Table 1, Fig. 1). Dose distributions for an example patient are shown in Fig. 3.

The reduction in lung dose with DIBH compared to FB translated into reduced median NTCP for radiation pneumonitis from 10.9 % to 9.4 % (Table 1). The NTCP was lower with DIBH for 90 % of the patients and the advantage was largest for the patients with highest risk of complications (Fig. 4a). NTCPs for mortality and acute esophageal toxicity were similar for FB and DIBH (Table 1).

3.2. Comparison of FB and DIBH in weeks 1 and 3

The number of recalculated plans with inadequate target coverage was similar for FB and DIBH. The clinical goal of CTV $V_{95\%}$ > 98 % was violated in 21 % of the 77 recalculated plans for FB, and 22 % for DIBH (Supplementary Table S4, Fig. 1d). For DIBH, this included 10 patients in w1 and 7 patients in w3, and for FB 8 patients in both w1 and w3. For 5 patients with DIBH and 2 with FB, the $V_{95\%}$ was < 98 % in both w1 and w3. Among 18 patients that had insufficient target coverage in one or more recalculated IMPT plans, 11 had an issue only with one of the breathing techniques at one time point.

CTV $V_{95\%}$ was < 95 % in 9 % of DIBH and 10 % of FB plans and < 90 % in 4 % of DIBH and 3 % of FB plans (Supplementary Table S4, Fig. 1d).

Table 1
Dose-volume parameters and NTCPs for nominal FB and DIBH IMPT plans at planning. Median values and 10th–90th percentiles (pctl) are presented, along with *p*-values for comparison between the techniques. The median of DIBH-FB differences and percentage of patients with a benefit of DIBH compared to FB are also given for each parameter.

Metric	FB		DIBH		DIBH-FB		*p*-value	Patients with benefit of DIBH
	Median	10th–90th pctl	Median	10th–90th pctl	Median	10th–90th pctl		
CTV $V_{95\%}$ (%)	100	100—100	100	100—100	0.0	—	0.3	–
Patient body D_{2cc} (%)	103.5	103.0—104.0	103.8	103.2—104.5	0.3	−0.1 — 0.8	<0.001	12 %
Lungs D_{mean} (Gy(RBE))	9.3	4.7—12.5	8.0	4.6—10.6	−1.3	−2.8 — −0.1	<0.001	90 %
Lungs $V_{5Gy(RBE)}$ (%)	26.1	15.8—35.6	23.8	14.7—34.5	−2.1	−5.8 — 0.9	<0.001	80 %
Lungs $V_{20Gy(RBE)}$ (%)	16.6	9.2—23.8	14.4	8.8—19.1	−2.3	−5.1 — 0.2	<0.001	88 %
Heart D_{mean} (Gy(RBE))	3.2	0.6—7.3	2.4	0.3—7.3	−0.1	−1.1 — 0.8	0.6	54 %
Heart $V_{5Gy(RBE)}$ (%)	9.2	2.8—20.8	10.0	1.6—23.4	0.6	−3.7 — 4.6	0.2	46 %
Heart $V_{30Gy(RBE)}$ (%)	4.2	0.6—10.5	3.1	0.1—9.5	−0.2	−1.9 — 0.7	0.06	54 %
Esophagus D_{mean} (Gy(RBE))	16.9	6.0—26.0	16.5	7.4—27.9	−0.4	−4.8 — 4.0	0.5	56 %
Esophagus $V_{20Gy(RBE)}$ (%)	31.3	11.1—49.7	29.6	15.4—50.3	−1.2	−8.2 — 7.0	0.9	51 %
Esophagus $V_{60Gy(RBE)}$ (%)	8.6	0.0—20.5	7.7	0.0—21.4	−0.2	−6.9 — 4.3	0.1	56 %
Spinal canal D_{max} (Gy(RBE))	29.4	11.1—45.5	28.2	9.5—44.1	−0.2	−9.9 — 5.5	0.2	54 %
Effective dose to immune cells (Gy (RBE))	2.5	1.6—3.3	2.2	1.4—3.1	−0.2	−0.5 — 0.0	<0.001	90 %
NTCP radiation pneumonitis (%)	10.9	4.8—19.6	9.4	3.6—16.8	−1.3	−3.7 — 0.0	<0.001	90 %
NTCP 2-year mortality (%)	39.8	31.0—51.2	40.4	31.0—52.5	−0.1	−2.1 — 1.4	0.3	51 %
NTCP acute esophageal toxicity (%)	32.9	8.7—49.2	31.6	12.7—51.4	−0.9	−8.4 — 6.8	0.5	56 %

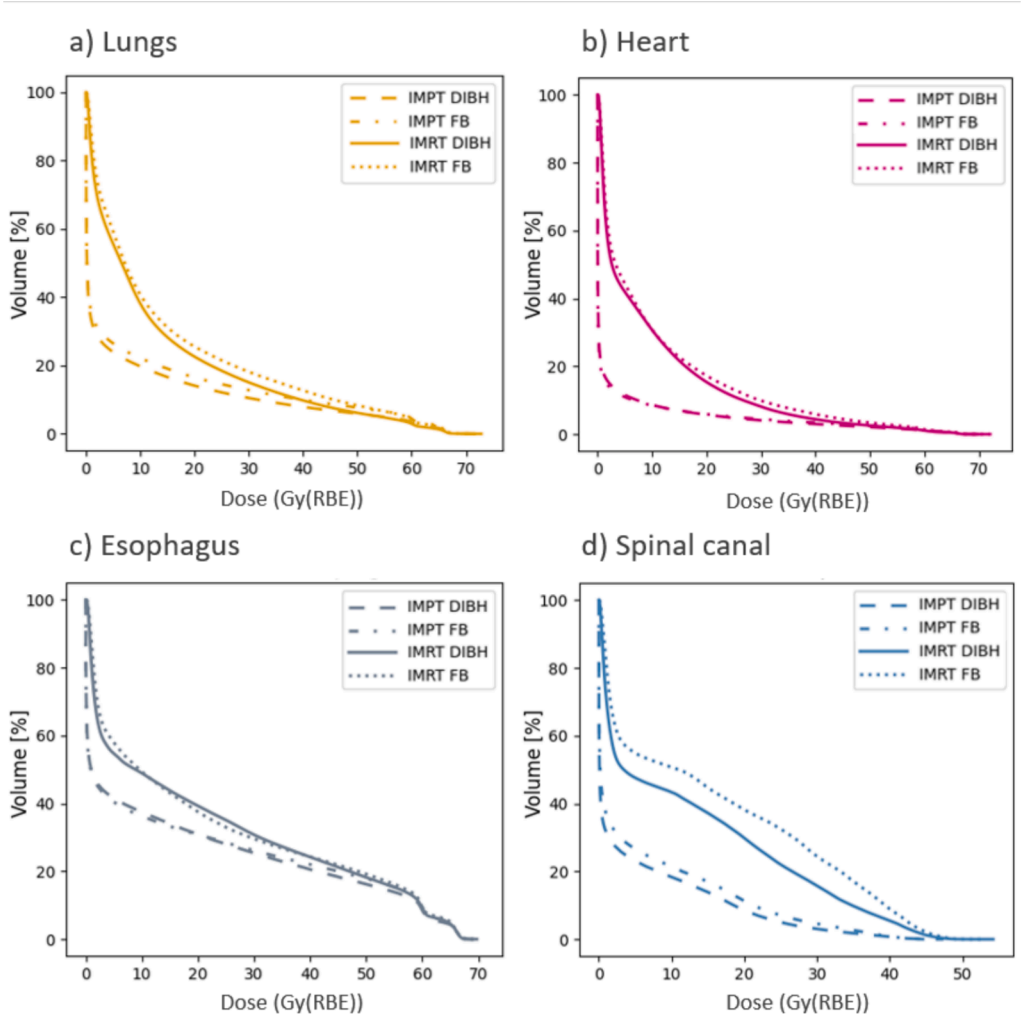

Fig. 2. Population average DVHs for organs at risk for the nominal planning scenario in the FB and DIBH plans, both for IMPT and IMRT.

In total 9 patients had $V_{95\%} < 95$ % in one or more recalculated plans, and the reasons for the missing target coverage were tumor growth (n = 3), baseline shift due to changed breathing pattern (n = 2), atelectasis resolved (n = 1), fixation error (n = 1), differences in delineation between planning and repeated CTs (n = 1) and a combination of factors (n = 1). The situation was slightly improved in w3 compared to w1,

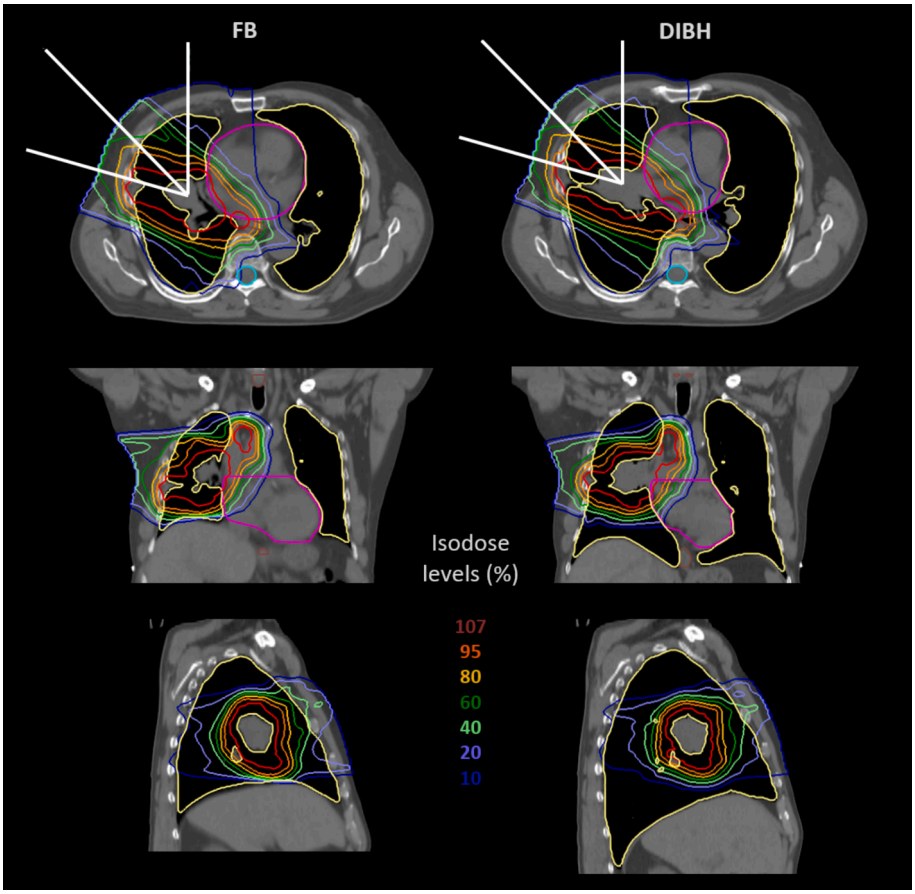

Fig. 3. Dose distributions for patient 12. Transversal (top), coronal (middle) and sagittal (bottom) views are shown for the FB (left) and DIBH (right) plans. Beam angles are indicated by white lines in the transversal views. Contours shown are CTV (red), lungs (yellow), heart (magenta), esophagus (brown) and spinal canal (cyan). Isodoses are relative to the prescribed dose of 60 Gy(RBE). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

possibly because tumor shrinkage improved target coverage for some patients.

Hot spots in the recalculated plans were not an issue; $D_{2cc} > 107$ % in the patient body was only observed for one patient. Both for FB and DIBH, the lung and heart dose in w1 and w3 remained similar to the dose at planning. The dose to the esophagus varied more and was on average lower than the planned dose in w1 and higher in w3 (Supplementary Tables S5-S6, Fig. 1a-c).

3.3. Comparison of IMPT and IMRT

CTV $V_{95\%}$ was > 99 % in the nominal scenario of all IMPT and IMRT DIBH and FB plans for all patients. Both for FB and DIBH, IMPT reduced the median D_{mean} to the lungs and heart by around 6 Gy and to the esophagus by around 3 Gy compared to IMRT. These differences were far larger than between FB and DIBH within each modality (Fig. 2). The same pattern was observed for NTCPs, with average reductions with IMPT compared to IMRT of around 9 pp for radiation pneumonitis, 10 pp for mortality and 7 pp for acute esophageal toxicity (statistical comparison of IMRT and IMPT in DIBH is given in Supplementary Materials S7). The NTCPs for radiation pneumonitis and mortality were lower with IMPT than IMRT for all patients regardless of breathing technique (Fig. 4).

Inter-fraction robustness of the target coverage was better in IMRT than IMPT; CTV $V_{95\%}$ was < 98 % in 5 % (DIBH) and 8 % (FB) of 73 recalculated IMRT plans, <95 % in 3 % of both DIBH and FB plans, and never < 90 %.

4. Discussion

In this study we compared DIBH to FB in IMPT of LA-NSCLC and showed that DIBH reduced the lung dose and risk of radiation pneumonitis compared to FB for 90 % of patients. Inter-fraction robustness of the target coverage was similar for both techniques. In addition, comparison of IMPT with IMRT showed far lower OAR doses with IMPT, both for FB and DIBH. Dose differences between IMPT and IMRT were much larger than differences between FB and DIBH.

There is little previous data on DIBH in proton therapy of LA-NSCLC. One treatment planning study with only 6 patients and no robustness measures suggested a potential for heart and lung sparing with DIBH compared to FB [21]. However, OAR doses in that study were much higher than in the current study, affecting the potential for dose reduction.

Inter-fraction robustness was comparable for FB and DIBH and most large deteriorations in target coverage were caused by anatomical changes or uncertainties that affected both techniques. Previous studies have found that more adaptions are necessary in proton therapy than IMRT [7,22]. In line with this, deterioration of target coverage was more frequent in the current study than our previous IMRT study [9]. However, many errors could be random and not require adaption; for 11/18 patients that were lacking target coverage, there was an issue only at one time point with one of the breathing techniques. Intra-fraction robustness was not investigated in the current study [23]. Interplay has limited impact on normofractionated treatment courses [24], as confirmed in a previous study by our group where a fraction dose of more than 90 % was maintained in all interplay simulations [6].

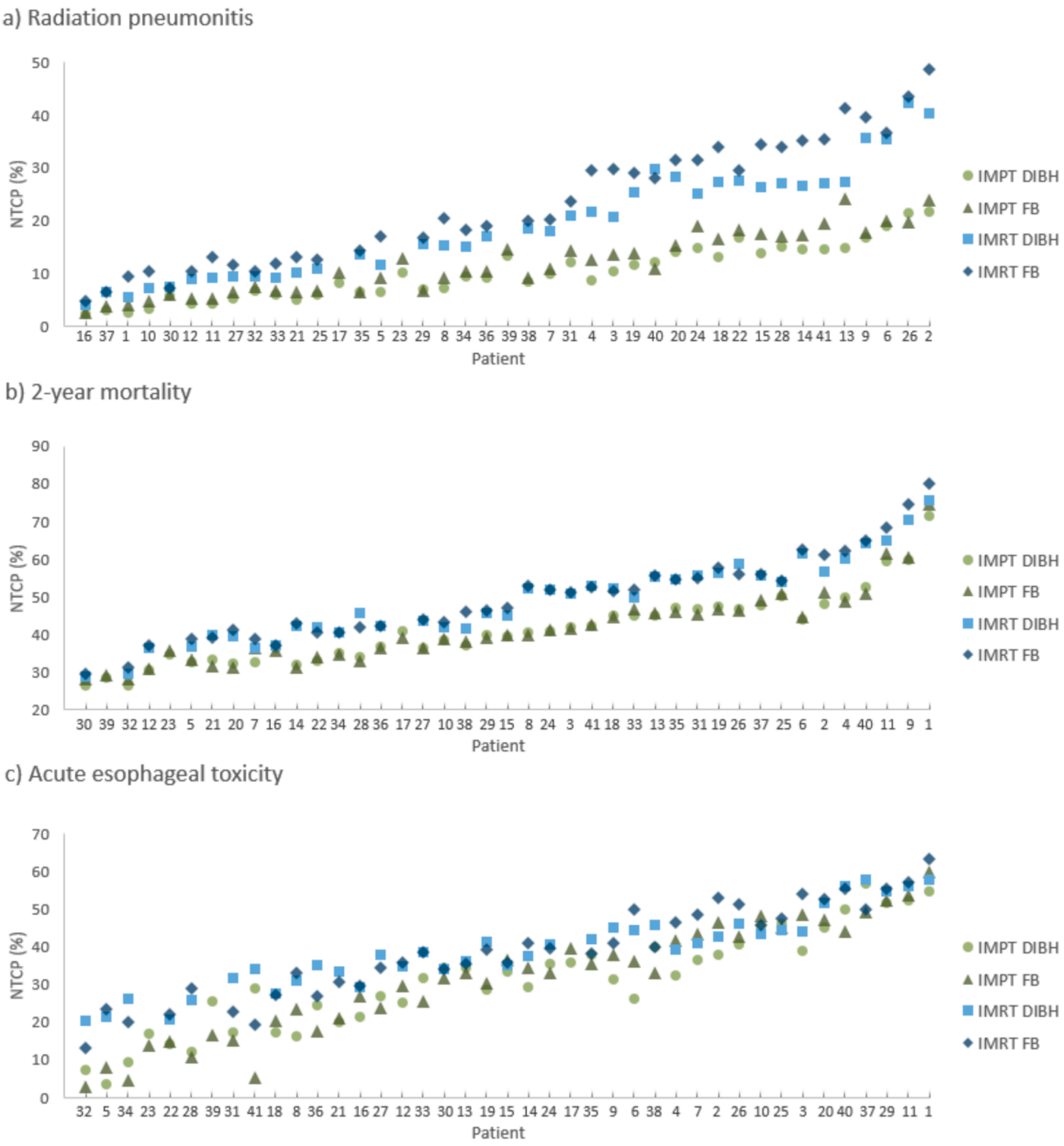

Fig. 4. NTCPs for a) radiation pneumonitis, b) 2-year mortality and c) acute esophageal toxicity for IMPT and IMRT plans in FB and DIBH for each patient. The patients are sorted according to the average NTCP for the four techniques in each plot, and patient numbers correspond to Fig. 1.

Based on previous studies, the number of breath holds required to deliver an IMPT fraction is expected to be in the same range as for IMRT [25,26]. In photon therapy, DIBH compliance among LA-NSCLC patients is high; Josipovic at el. reported that 94 % of patients who started treatment in DIBH were able to finish, while 6 % switched to FB [27].

Compared to IMRT, IMPT in both FB and DIBH greatly and consistently reduced NTCPs and dose to all investigated OARs. The relative reduction in lung D_{mean} with DIBH compared to FB was 14 % with IMPT, compared to 9 % in our previous IMRT study [9]. This increase in the lung sparing potential with DIBH in IMPT could be explained by the ability of protons to stop sharply at the distal tumor edge, allowing sparing of the contralateral lung at the level of the tumor, while in photon therapy, sparing with DIBH can mainly be achieved cranially and caudally to the tumor. The heart sparing effect of DIBH seen in IMRT was not present in IMPT. However, heart doses in IMPT were generally very low, limiting the room for improvement.

Regardless of breathing technique, OAR doses in the current study were low compared to previous reports on proton therapy of LA-NSCLC. In clinical studies, both using passive scattering proton therapy and IMPT, reported average mean doses to the lungs have been around 13–16 Gy(RBE), to the heart 5–10 Gy(RBE) and to the esophagus 18–28 Gy(RBE); some of these studies had lung and heart doses more than

twice as high as in the current study [5,28–30]. This indicates a potential for increased clinical benefit of IMPT that should be further investigated. There are several possible explanations for the differences in reported OAR sparing in the literature. Autoplanning facilitates OAR dose reduction in photon therapy and could be even more beneficial in IMPT due to the complexity of treatment planning and relative novelty and limited experience with IMPT [31]. Beam configuration is highly important in proton therapy, and the same individually selected beam angles were used in both IMPT plans for each patient in this study to limit the influence on the results. When evaluating earlier studies, it is important to bear in mind that proton machines, treatment techniques and optimization algorithms are rapidly evolving. The potential of current proton therapy, in particular IMPT, compared to mature photon techniques could be greater than shown so far.

Autoplanning allows efficient and bias-free generation of treatment plans and was essential for creating 82 IMPT plans for this study. Lacking commercially available tools for high-quality, robust, automated IMPT planning, scripted treatment planning in a commercial TPS using an in-house developed script was chosen. The feasibility of scripted treatment planning for LA-NSCLC could be different in photon and proton therapy. With photons, there is more potential for adjusting the dose distribution by moving dose away from specific areas. With IMPT, the spread of low and medium dose is limited and there are fewer compromises to be made by the planner, which could make scripting the planning process less complex. The developed script performed well in preliminary validation compared to manually created plans and will be further developed and investigated in other cohorts and treatment sites. Tasks such as image registrations and recalculations were also automated, making comprehensive robustness analyses feasible for a fairly high number of patients.

Limitations of this study include use of NTCP models not validated for IMPT or DIBH. The radiation pneumonitis model is based on 3D-CRT data, but has been validated for proton therapy [32]. The model for acute esophageal toxicity is based on IMRT/VMAT data, and the mortality model is based on data from 3D-CRT, VMAT and hybrid VMAT treatments, without validation for proton therapy. The applied models are currently used for patient selection for proton therapy in the Netherlands [14]. IMPT and IMRT plans compared in the current study were all created automatically, but with different autoplanning methods in different treatment planning systems.

In conclusion, DIBH and FB IMPT plans for LA-NSCLC patients were generated using an in-house developed autoplanning script and compared in terms of dose parameters and NTCPs. Lung dose and risk of radiation pneumonitis were significantly reduced with DIBH. DIBH and FB showed similar inter-fraction robustness. Compared to IMRT, IMPT in both FB and DIBH gave substantial NTCP reductions. The low OAR doses obtained compared to previous IMPT reports underline the potential of automatically optimized robust IMPT plans for treatment of LA-NSCLC.

CRediT authorship contribution statement

Kristine Fjellanger: Conceptualization, Formal analysis, Investigation, Methodology, Software, Funding acquisition, Visualization, Writing – original draft, Writing – review & editing, Validation. **Ben J. M. Heijmen:** Conceptualization, Methodology, Writing – review & editing, Supervision. **Sebastiaan Breedveld:** Conceptualization, Methodology, Writing – review & editing. **Inger Marie Sandvik:** Methodology, Resources. **Liv B. Hysing:** Conceptualization, Funding acquisition, Methodology, Project administration, Resources, Supervision, Writing – review & editing.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: BJMH, SB: Erasmus MC Cancer Institute has research collaborations with Elekta AB (Stockholm, Sweden), Accuray, Inc (Sunnyvale, USA) and Varian Medical Systems, Inc (Palo Alto, USA). The other authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.phro.2024.100590.

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